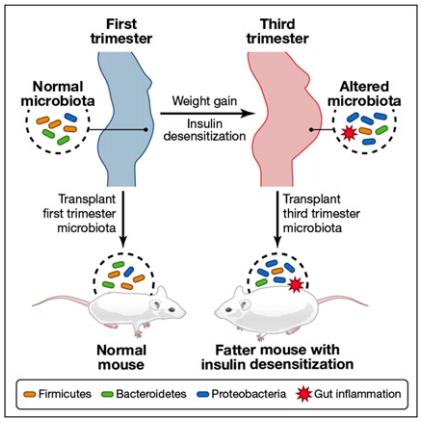
In This Issue

Cell



Moms, Microbes, and Metabolism

PAGE 470

Pregnancy is accompanied by metabolic changes such as higher blood sugar, insulin resistance, and weight gain that can promote the growth of the fetus and newborn. Koren et al. now examine the alterations to the gut microbiome during pregnancy and provide evidence that the distinctive microbiome associated with the third trimester can induce the metabolic changes seen in pregnancy. The authors propose that the host-microbiome interactions that can lead to detrimental aspects of metabolic syndrome may have roots in interactions that benefit fetuses and newborns.

In-Depth Look at Human Diversity

PAGE 457

Whole-genome sequencing of 15 individuals in 3 different hunter-gatherer populations in Africa uncovers 13.4 million variants, including ~3 million variants not currently present in existing databases. The sequencing data also provide evidence of archaic introgression in all three populations and reveal numerous loci that harbor signatures of local adaptation, including those that play a role in growth and pituitary function within the Pygmy population.

Brambleberry Unites Pro-Nuclei

PAGE 521

During early embryogenesis, when cells are large, individual chromatin masses are surrounded by nuclear envelope. How these structures, called karyomeres, fuse to form a single nucleus has been unclear. Now, Abrams et al. identify Brambleberry as a new nuclear envelope protein that dynamically assembles to mediate karyomere fusion. The authors also provide a molecular handle for investigating some fertility defects as Brambleberry foci mediate pronuclear fusion following fertilization.

Exome Sequencing Links DNA Damage to Ciliopathies

PAGE 533

Whole-exome sequencing of individuals with retinal-renal ciliopathies enabled Chaki et al. to identify two new causative alleles for this family of disorders. They find that these genes are also involved in DNA damage response (DDR) signaling. These proteins are shown to localize not only to centrosomes, as expected for ciliopathies, but also to nuclear foci with other DDR components. This provides new insight into the pathogenic mechanisms behind this class of degenerative disorders.

HSF1's Non-Heat-Shock Hat in Tumors

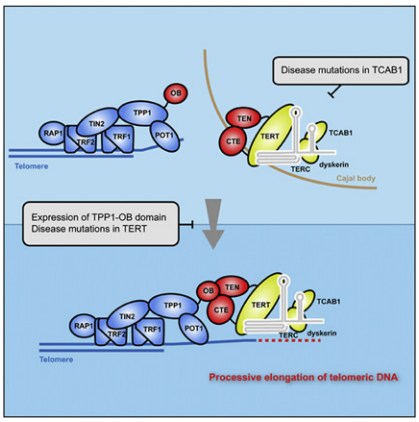
PAGE 549

The heat-shock response transcription factor HSF1's oncogenic role had been thought to be a result of its ability to trigger the heat-shock response, including the upregulation of chaperones and other proteins that allow cells to cope with stress. Now, Mendillo et al. show that HSF1's purview extends far beyond heat shock in tumor cells, and the newly identified targets, which include regulators of cell cycle, signaling, metabolism, and adhesion, appear to play a key role in determining cancer aggressiveness.

Manipulating Megakaryocyte Endocytosis

PAGE 575

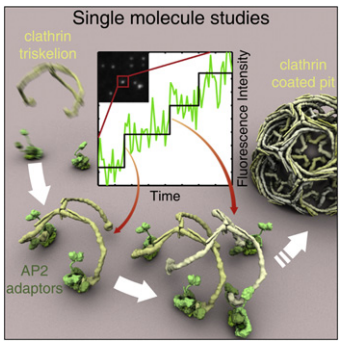
Megakaryocytes undergo a modified form of the cell cycle termed endomitosis, in which cells skip the late stages of mitosis to become polyploid. Using a chemical screening approach, Wen et al. now provide insight into the protein kinase networks that regulate endomitosis. In addition, one of the compounds from the screen selectively increased polyploidization and apoptosis of malignant megakaryocytes, revealing a therapeutic strategy for the treatment of acute megakaryocytic leukemia.



Telomerase Recruiter

PAGE 481

Zhong et al. show that TPP1, a telomere-binding protein, recruits telomerase to telomeres. Direct interaction between TPP1's OB domain and TERT is necessary for telomere maintenance and sufficient for recruitment to DNA. Disrupting the association leads to accumulation of telomerase in Cajal bodies. Human disease mutations in TERT associated with pulmonary fibrosis block telomerase recruitment from the Cajal bodies and implicate a localization defect in the disease pathogenesis.



Endocytosis Flipbooks

PAGE 495 and PAGE 508

Formation of clathrin-coated pits for endocytosis requires the organized recruitment of hundreds of protein molecules. Cocucci et al. use live-cell imaging combined with statistical modeling to examine the initial steps of this process at a single-molecule resolution in mammalian cells. They show that clathrin coat assembly initiates with two sequential steps, each involving the arrival of one clathrin triskelion and two AP2 adaptors. In addition, they find that the accessory molecules required for initial assembly are distinct from those required for maintenance. Kukulski et al. employ correlated fluorescence and electron microscopy to study the early stages of endocytosis in yeast. They relate specific changes in the membrane shape with the dynamics of endocytic protein machinery and show that actin polymerization rather than clathrin recruitment initiates the initial membrane bending.

Blood and Heart: One Degree of Separation

PAGE 590

The transcription factor Scl promotes the development of hematopoietic stem/progenitor cells from the hemogenic endothelium during embryogenesis. Van Handel et al. now show that Scl also represses cardiomyogenesis: in the absence of Scl, the endothelium generates spontaneously beating cardiomyocytes. These results reveal broad developmental potential in the embryonic endothelium that is governed by Scl.

The Bell Tolls for Septic Shock

PAGE 606

Rathinam et al. discover that, in response to infection with Gram-negative bacteria, TLR4 signaling leads to activation of the NLRP3 inflammasome. TLR4 allows TRIF to cause IFN production, which in turn induces caspase-11. The identification of TRIF as a component of caspase-11-dependent NLRP3 inflammasome activation highlights the central role of TLRs as master regulators of the NLRP3 inflammasome and unveils new targets for therapeutic intervention in septic shock.

A Combination Approach to Obesity Treatment

PAGE 620

White adipocytes store energy, whereas brown adipocytes use energy to generate heat. Qiang and colleagues now show that activation of the deacetylase SirT1 confers "brown-like" features on white adipocytes via deacetylation of the nuclear receptor Pparγ, a key regulator of adipogenesis and also a target of the TZD class of diabetes drugs. The data raise the possibility of using SirT1 agonists with lower-dose TZD, which may reduce adverse effects, as combination therapy to fight obesity.

Parsing Pools of Neuronal Receptors

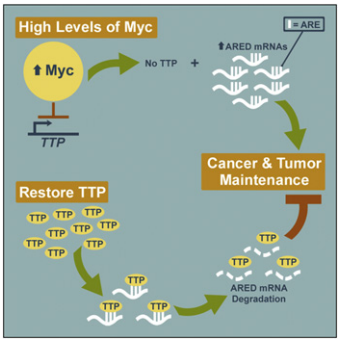
PAGE 633

NMDA receptors are found on the neuronal membrane both within synapses and outside of the synaptic regions. Papouin et al. find that these two classes of NMDARs are gated by different amino acids. This differential gating enabled dissection of distinct functional roles for each pool of receptors and led to the surprising finding that glutamate toxicity and long-term potentiation are mediated solely by synaptic NMDARs. The findings challenge the widespread view that extrasynaptic NMDARs are important for excitotoxicity.

Tuning TFs for Synthetic Wiring

PAGE 647

Synthetic approaches to rewire and construct complex transcriptional networks in eukaryotes have been hindered by lack of reliable components and frameworks for assembling them. Now, Khalil et al. use artificial zinc fingers to wire orthogonal connections in synthetic transcriptional circuits in yeast. Synthetic transcription factor component properties can be independently or combinatorially adjusted to modulate outputs and reshape signal integration. This approach represents a new standard for how to engineer transcriptional networks in eukaryotes.



mRNA Destabilizer Disables Tumorigenesis

PAGE 563

Many short-lived mRNAs harbor AU-rich elements that enable regulation by AU-binding proteins (AUBPs). Rounbehler et al. show that Myc oncoproteins regulate the transcription of several AUBPs, thus indirectly regulating multiple AU-containing mRNAs. Importantly, activation of one such AUBP, the RNA-destabilizing Tristetraprolin (TTP), counteracts the development and maintenance of Myc-induced cancer, establishing TTP as a tumor suppressor and a potential target for therapeutic intervention.